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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/010,154	12/10/2001	Ryusuke Nakagiri	2139.27	2545
5514 7590 10/26/2007 FITZPATRICK CELLA HARPER & SCINTO 30 ROCKEFELLER PLAZA NEW YORK, NY 10112				
			EXAMINER KISHORE, GOLLAMUDI S	
			ART UNIT 1615	PAPER NUMBER
			MAIL DATE 10/26/2007	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/010,154	Applicant(s) NAKAGIRI ET AL.
	Examiner Gollamudi S. Kishore, Ph.D	Art Unit 1615

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10 October 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 43 and 44 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 43 and 44 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The amendment dated 1-25-07 is acknowledged.

Claims included in the prosecution are 43-44.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 43-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant amends claim 43 to recite 'inhibiting hepatonecrosis'. There is no support for this expression in the specification as originally filed and therefore, deemed to be new matter.

3. Claims 43 and 44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d, 1400 (Fed.Cir.1988). Among these factors are: (1) the nature of the

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invention; 2) the state of the prior art; 3) the relative skill of those in the art; 4) the predictability or unpredictability of the art; 5) the breadth of the claims; 6) the amount of direction or guidance presented; 7) the presence or absence of working examples; and 8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

1) The nature of the invention: the invention concerns with inhibiting hepatonecrosis using hydrangea extracts.

2) The state of the prior art: the state of the prior art is very high in terms of the effect of these extracts on free radicals.

3) The relative skill of those in the art: the skill of one of ordinary skill in the art is very high (Ph.D level technology).

4) The predictability or unpredictability in the art: hepatonecrosis can be caused by a variety of factors, which include chemicals as well as viruses. Just because the claimed extracts have an effect on a liver enzyme by a single injection of a chemical one cannot predict the extract's effect on the inhibition or prevention of hepatonecrosis caused by a variety of agents.

5). The breadth of the claims: instant claim is very broad in terms disease to be prevented. As pointed out above, hepatonecrosis can be caused by a variety of agents

6) The amount of direction of guidance provided: instant specification provides no guidance at all in terms of inhibiting or preventing the hepatonecrosis itself which could be due to a variety of factors.

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7) The presence or absence of working examples: as pointed out above, the only examples includes some in vitro studies and an in vivo study wherein a liver enzyme is measured after a single injection of a chemical which is not indicative of the prevention of hepatonecrosis itself.

8) The quantity of experimentation necessary: as pointed out above, hepatonecrosis can be due to different causes and instant claims are drawn to inhibition (prevention) of hepatonecrosis. It would require undue experimentation to determine how long the composition has to be given, the amount necessary and the protocol of administration.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. Claims 43-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thiele et al (5,939,535) in combination with Karmali (6,184,227) and Yamahara et al (Nature Medicines, 1995), JP 10046142 (both are of record), the last two references by themselves or together.

Thiele et al disclose that alcohol causes increase in the levels of lipid peroxidation, acetaldehyde and malondialdehyde, which cause liver injury. According to Thiele et al, malondialdehyde is formed by the peroxidation of polyunsaturated fatty acids and from the oxidative degradation of deoxyribose by a hydroxy free radical (col. 1, line

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15 through col. 2, line 40). What is lacking in Thiele et al is the protection of the liver function from damage from excessive consumption of alcohol.

Karmali discloses that the administration of antioxidants inhibits the oxidation of ethanol and the toxic effects of acetaldehyde (col. 3, line 45 through col. 4, line 22). Karmali however, does not teach the administration of ethanolic extracts of Hydrangea.

Yamahara et al disclose that the methanol extract of Hydrangea Dulcis Folium exhibits strong radical inhibiting effect and inhibitory effect on oxidation of lipids (page 2, lines 7-9 and Experiment on pages 2-6 of the English translation).

JP discloses extracts of Saxifrage stolonifera exhibit marked and potent antioxidant effect compared to conventional antioxidants (English abstract).

In essence the references of Thiele et al and Karmali show the increases in lipid peroxidation and the production of reactive aldehydes caused by ethanol consumption and the inhibitory effect of antioxidants on the lipid peroxidation and the production of reactive aldehydes. It would have been obvious to one of ordinary skill in the art to use the extracts of Hydrangea Dulcis Folium or Saxifrage in the teachings of Thiele et al and Karmali to protect the liver function from alcohol since the references of Yamahara et al and JP teach the strong inhibitory action on the free radicals exhibited by these extracts.

Applicant's arguments have been fully considered, but are not persuasive.

Applicant's arguments that those of ordinary skill in the art are also well aware that liver injuries such as hepatonecrosis cannot be protected only by inhibiting lipid peroxidation as evidenced by Suzuki reference. This argument is not persuasive. A careful review of the publication by Suzuki (English translation) indicates that Suzuki's studies are

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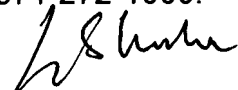
concerned only with carbon tetrachloride induced liver injury and specific to this agent. Instant claims do not recite any specific cause of the hepatonecrosis. Suzuki in the last paragraph on page 5 (English translation) clearly state "That is to say, CCl₄-induced liver injuries may involve a factor other than lipid peroxidation". This does not mean that other agents, which cause hepatonecrosis, involve other factors just as CCl₄ caused liver injury. Furthermore, a careful review of instant specification indicates that applicant measures the enzyme GPT after a single injection of galactosamine in one in vivo experiment. The rest of applicant's experiments are only in vitro studies. The scope of the claims is not commensurate with the studies reported.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Woodward Michael can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Gollamudi S Kishore, Ph.D
Primary Examiner
Art Unit 1615

GSK